PRELIMINARY STATEMENT TO BMJ PANEL AND INITIAL RESPONSE TO DR. COLLINS' CONCERNS

Introduction

The BMJ analysis article "Should people at low risk of cardiovascular disease take a statin?" represents an important attempt to calculate the real world benefits and harms from the use of statins for primary prevention. It criticizes the view of the CTT group and the recent Cochrane review promoting use of statins for this population an argues that the evidence (relying necessarily upon CTT data) shows that people with a 10 year risk of less than 20% will derive no overall benefit from statin therapy, that the risk of harm is not known precisely but is certainly greater than 0, and therefore that prescribing guidelines should not be broadened to include people with < 20% 10-year risk of ASCVD.

The bulk of the article identifies the reasons that the benefits of statins for primary prevention are likely exaggerated and that the real benefits are of such a low magnitude (with no reduction in overall mortality or overall serious illness) that the majority of people who understood the small chance of benefit (in decreased risk of non-fatal heart attack) would not take the drug even if there were no harms. The rest of the article was designed to make it clear that statins are not risk free and they can cause harm. It was not possible in the space allotted to be comprehensive in terms of all of what is known about statin harms. We agree that it is difficult to assess the magnitude of the harms from observational studies and that the magnitude of harms with statins is uncertain and debatable at this time. We feel that the correction that is published on the BMJ website is sufficient to correct the inaccuracy in the article.

However, because of the importance of the message that for people with a 10-year risk of < 20%, statin therapy does not reduce mortality or total serious adverse events, it is essential that the article not be retracted.

The issue clearly has important consequences for patients and it will probably be many years before we have a better idea of the magnitude of the harms from long-term statin use. At this time an open debate of the scientific issues is the only approach that is in the best interests of the public. We welcome such an open debate.

What follows is a brief response to Rory Collins' request for retraction, which we received yesterday so have not had enough time to fully evaluate. The headings are from his communication.

Serious misrepresentation of evidence about rate of side-effects

caused by statins

We agree with Dr. Collins that the findings by Zhang et al with regard to the frequency with which people in their observational study reported the discontinuation of statin therapy due to adverse events was interpreted erroneously in our paper. They reported that 17.4% of people (in unstructured routine follow-up visits) reported statin related events. And further, that up to 9% of patients treated with statins discontinued their statin therapy because of statin-related adverse events (the imprecision is due to potential inaccuracies of default categorization in electronic medical records). We agreed to correction as soon as this error was brought to our attention.

Given the constraints of space, we did not address in our BMJ article (but in retrospect probably should have) that of 107,835 statin-treated patients followed in routine care settings over 8 years in the study by Zhang et al, more than half, 57,292 discontinued their statin therapy at least temporarily. Because the routine follow-up visits were unstructured—without specific query about muscle symptoms, cognitive changes, sexual difficulties, fatigue, etc—the rate of ascertainment of such symptoms and capture in electronic medical records is unknown. The true rate of statin-related side effects among the 57,292 people who discontinued statin therapy is not known.

Further, Dr. Collins expresses concern that in our correction we misrepresented Zhang et al in our statement:

> *"…as many as 87% of statin discontinuations among patients with documented statin-related events could have been due to these events"*

However, the language of our correction is consistent with the text of Zhang et al:

> Overall, as many as 87% of statin discontinuations among patients with documented statin-related events could have been due to these events.

Dr. Collins writes that the evidence in the paper by Zhang et al does not support the claim "that statins cause side effects in 18-20% of patients." In fact Zhang et al do not use the word "cause" but do report such occurrence:

> The rate of reported statin-related events to statins was nearly 18%, substantially higher than the 5% to 10% rate usually described in randomized, placebo-controlled, clinical trials (24). **This finding is consistent with previously published observational studies** (28-31). Similar to both clinical trials

> and observational studies (23, 32), musculoskeletal symptoms were predominant, accounting for 40% of statin-related events. Overt rhabdomyolysis was found in only 0.006% of the study patients, also consistent with previous reports that statin-induced myopathy is rare (33). [Emphasis added]

Because we had no cite other than Zhang to support the fourth bullet in the box at the end of our article was withdrawn:

> The side effects of statins—including muscle symptoms, increased risk of diabetes (especially in women), liver inflammation, cataracts, decreased energy, sexual dysfunction, and exertional fatigue—occur in about 20% of people treated with statins.

Had we simply aligned our language with that of Zhang et al above by adding the bold language below, the bullet would have been substantiated by Zhang et al:

> The side effects of statins—including muscle symptoms, increased risk of diabetes (especially in women), liver inflammation, cataracts, decreased energy, sexual dysfunction, and exertional fatigue—occur in about 20% of people **in published observational studies** treated with statins.

Dr. Collins discussed with the Editor on May 8 2014 the fact that rates of statin-related side effects are equal in statin and placebo groups. This claim does not take into account that, for example, the largest of all studies included in the CTT meta-analysis—the Heart Protection Study with 20,536 patients (of which Dr. Collins is the lead author)—included a screening phase, which excluded more than half of volunteers, then a run-in phase that involved 4 weeks of placebo followed by 4-6 weeks of fixed dose simvastatin 40 mg daily. More than one third of those who passed the initial screening were later either deemed not eligible or withdrew in the process of the run-in period. Thus, patients with early side effects were preferentially removed from the randomized study population, minimizing the rate of adverse events during the study period and compromising the external validity of the results with regard to adverse event experiences.

Evidence against the magnitude of the side-effect rate claimed in the BMJ articles

Simply because the CTT protocol of 1994 did not include serious adverse events in toto does not remove this standard indicator of the rate serious illness/adverse events that occur during the course of a study. Because SAE recording and reporting are standard in Clinical Study Reports, and because of their comprehensive overview

of study events, it is reasonable to expect that CTT would report SAEs in total rather than limiting their reporting of SAEs to the subset of non-vascular death and site-specific cancer.

With regard to cause-specific mortality, data reported in Webfigure 8 that accompanied the 2012 CTT meta-analysis published in *Lancet* show that statin therapy did not reduce CHD deaths for those with < 5% or those with ≥ 5%, < 10% 5-year risk. Further, Mantel Haenszel adjusted RR does not show significant reduction in CHD mortality for the two groups combined. Webfigure 8 shows similar results for stroke mortality. Neither is there a significant reduction in CHD and stroke mortality combined associated with statin therapy for people with < 10% 5-year risk (equivalent to < 20% 10-year risk).

It would not be consistent to restrict SAE reporting to "treatment specific" problems, without reporting treatments specific (i.e. CHD and stroke) death rates associated with statin treatment in low risk patients.

Centrality of the misleading claims about side-effect rates to these papers

Dr. Collins points our attention to Webfigure 8 rather than Figure 3 of the *Lancet* publication for all-cause mortality data. Like the calculation we presented in our BMJ Analysis piece, data from Webfigure 8 show no significant reduction in all-cause mortality for neither those with < 5% nor ≥ 5%, < 10% 5-year risk. Further, Prof. Jewell has recalculated the Mantel-Haenszel calculation for the two groups combined and found, as in our BMJ article, there is not a significant reduction associated with statin therapy for the two groups combined, RR 0.92, 95% CI 0.84-1.01).

- ***Misleading comparisons of myopathy and myalgia rates***

The following is a summary of the myopathy vs. muscle pain/symptoms issue as our article went through peer review. (This issue was also raised by Dr. Liam Smeeth in the recent Sunday Times.)

The paragraph from our original manuscript submitted to BMJ:

> CTT data from clinical trials show the excess risk of myopathy associated with statin therapy is 0.5 per 1000 patients over 5 years. However, a cross-sectional analysis from the National Health and Nutrition Examination Survey (NHANES) database shows that the frequency of muscle symptoms associated with statin use is 100 times greater—53 per 1000 patients[1] —than reported in clinical trials.

[1] Buettner CA, Davis RB, Leveille SG, et al, Prevalence of Musculoskeletal Pain and Statin Use, Journal of General Internal Medicine, 2008; 23:1182–6

Liam Smeeth commented in his peer-review:

> 2. The results presented for myopathy are misleading. NHANES focused on ascertaining symptoms from people exposed to statins. Muscle pain is incredibly common in the general population and is thus incredibly common among people both treated and not treated with statins. In the randomised Heart Protection Study, almost one third of people in both arms (i.e. including the placebo arm) complained of muscle pain and the effect estimate was 0.99 (95% CI 0.95 to 1.03). Serious rhabdomyolysis was rare: 5 cases in the 10,269 allocated tosimvastatin and 3 cases in the 10,267 allocated to placebo.

In the published article we clarified the difference in outcome measures of "myopathy" in CTT's publication, specifically stating "muscle pain" (rather than muscle symptoms) in the NHANES data:

> The excess risk of myopathy associated with statins reported in the CTT meta-analysis is 0.5 per 1000 patients over five years—number needed to harm (NNH) is 2000. However, a cross sectional analysis from the National Health and Nutrition Examination Survey database shows that the **prevalence of muscle pain** in statin users is 50% greater than in non-users. In absolute terms, this increase in muscle pain is 100 times greater than that reported in clinical trials—53/1000 patients, NNH=19.13. [Emphasis added]

In the above paragraph, we clarified the difference between the CTT's definition of myopathy and the NHANES endpoint of muscle pain. The point we were making was that one out of twenty real people at low risk of CV disease will experience muscle pain as a result of taking a statin, from which they will derive no overall benefit.

Trial in the public media:

Dr. Collins actually conflated myopathy with muscle weakness in a quote that appeared in The Guardian March 14, 2014:

> "We have really good data from over 100,000 people that show that the statins are very well tolerated. There are only one or two well-documented [problematic] side effects." Myopathy, or muscle weakness, occurred in one in 10,000 people, he said, and there was a small increase in diabetes.

And,

> "It is a serious disservice to British and international medicine," he (Rory) said, claiming that it was probably killing more people than had been harmed as a result of the paper on the MMR vaccine by Andrew Wakefield.

Dr. Collins conflation of serious myopathy with more common muscle symptoms was repeated on BBC:

> There have been over 100,000 patients in trials where they get either placebo or active therapy. There is a **very, very low risk of muscle problems**, there is a small increase in diabetes, but these are far outweighed in the high-risk patients, and indeed, even in the patients at lower risk – they are being considered by NICE by the reductions in the risks of heart attacks and strokes. BBC News audio, Today Programme, May 15, 2014 [Emphasis added]

Several newspaper stories referred to unnecessary deaths that would result from the BMJ article, despite the article showing no reduction in deaths for people with < 20% 10-year risk. For example,

> A report published in the British Medical Journal said the cholesterol-lowering drugs, taken by eight million Britons, cause side-effects such as liver and kidney disease and diabetes in one in five patients.
>
> Parts of the article were withdrawn last week, following repeated criticism from an Oxford University academic that the risks had been exaggerated up to 20-fold.
>
> Sir Rory Collins said the figure is one in 100 and **described the published claims as a 'huge error' that will 'cause unnecessary deaths' by discouraging patients from taking the medicine.** Mail Online, May 19 2014 [Emphasis added]

Conclusion

Given that CTT data show that statins provide no overall mortality benefit and no reduction in serious illness for people with < 20%, the issue of side effects is of critical importance. Questions of accurate ascertainment, RCTs (some of which screen out those with side effects during a run-in period, e.g. the Heart Protection Study on which Prof. Collins is the lead author) vs observational data, and accurate determination of numerators and denominators when determining rates of adverse events are

sufficiently nuanced that we wonder whether this calls for a short new piece outlining the subtleties and perhaps touching on the diabetes issue?

Further, all of the evidence upon which we have relied has, by necessity come either from the manufacturer-sponsored studies or CTT's interpretation of those studies. Without access to patient-level data, this cannot be considered "evidence-based" analysis. Therefore, we call for the release of the data by the manufacturers so that the public can be confident that the benefits and risks of statin therapy have been verified beyond the context of conflicts of interest.

Potential Conflicts of Interest: John Abramson and Nicholas Jewell serve as experts in litigation, including a case involving the association between Lipitor and new onset diabetes in women. John Abramson also delivers lectures to non-profit (primarily educational) institutions for which he receives payment.